# Fundamentals of Biophysics

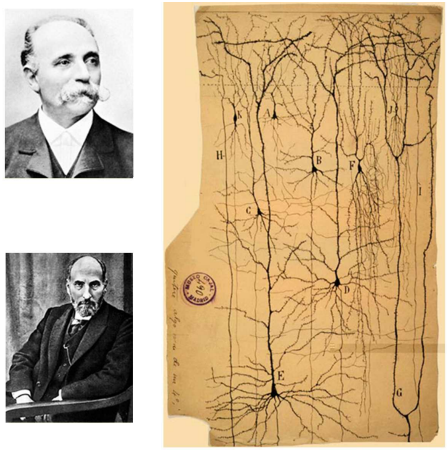
pass

# 1. The Passive Isopotential Cell

pint

## 1.1. Introduction

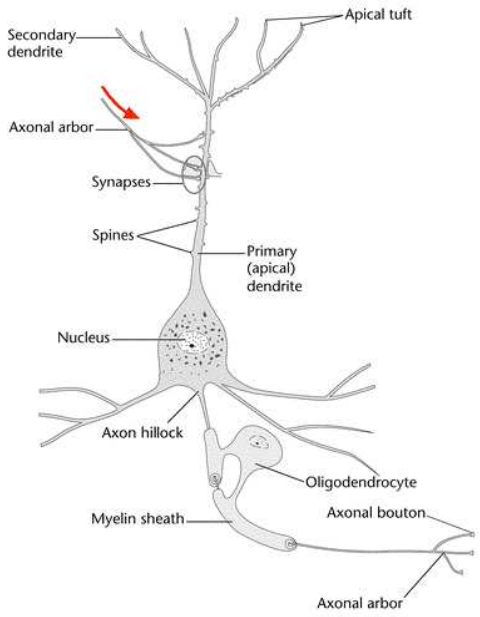
Modern neuroscience can be traced back to work of Camillo Golgi, an Italian physician and scientist who invented around the end of the 19th century a method allowing to stain randomly and sparsely neurons, the cells constituting the elementary building blocks of all nervous systems. This anatomical method is now called the Golgi stain in his honor. The Spanish neuroanatomist Santiago Ramón y Cajal first took advantage of the Golgi method to systematically describe the different types of neurons contained in the brain of many animal species (fig. 1.1). His work founded modern neuroscience by showing that neurons typically consist of several distinct compartments: the soma that contains the cell nucleus and its genetic code, the axon that allows electrical signals to propagate to other downstream neurons and the dendrites where a neuron typically receives inputs from other, upstream neurons through electrical or chemical synapses. The electrical signals that propagate along the axon are generated at the axon hillock whereas the dendrites of several types of neurons contain small protuberances called spines where synapses are often localized (fig. 1.2).




gc

**Figure** 1.1. Portraits of Camillo Golgi (top) and Santiago Ramón y Cajal

(bottom) and drawing of cortical pyramidal cells from Cajal (right).

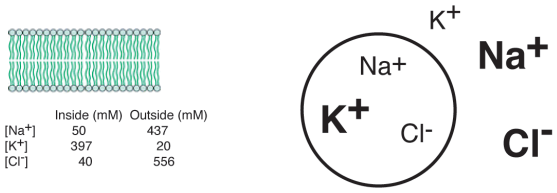



pyr

**Figure** 1.2. Schematic illustration of a pyramidal neuron and its main compartments.

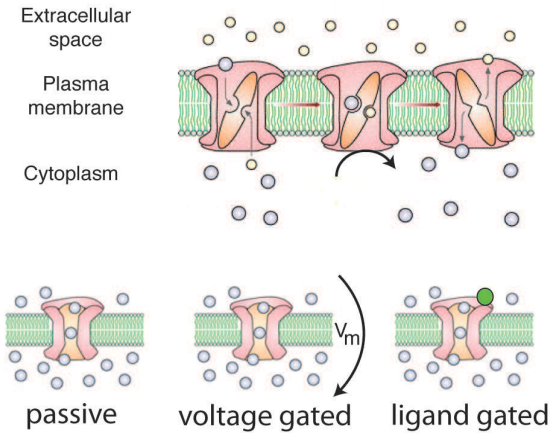
The neuron is isolated from the extracellular space by the cell membrane, a lipid bilayer that acts simultaneously as an electrical insulator and as an electrical capacitor, meaning that it is able to store electrical charge. A fundamental property of neurons is that the concentration of ions in the acqueous solution that constitutes the cell intracellular fluid, or cytoplasm, is different from the concentration in the extracellular space (fig. 1.3). This difference is maintained by a battery of specialized proteins embedded in the cell membrane called exchangers and pumps. Exchangers and pumps are able to shuttle ions in or out of the cell at the expense of energy. In addition, other proteins embedded in the membrane act as channels, allowing specific ions, such as sodium, potassium or chloride to move in or out of the cell. The simplest ones that we will study first exist in a single, open state, always allowing ions to flow across them. More complex channels can be either closed or open, with their opening controlled either

by the presence of specific chemicals such as neurotransmitters that bind to them or by changes in the electrical potential across the membrane (fig. 1.4).




rest

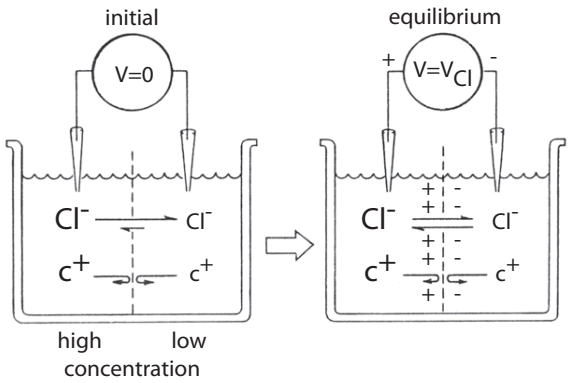
**Figure** 1.3. The lipid bilayer membrane is illustrated on the left along with ion concentrations (in millimoles per liter, mM) typical of the giant squid axon, a neuron responsible for fast escape responses. Accordingly, the diagram on the right illustrates the typical relative ionic concentrations inside and outside a neuron.




chans

**Figure** 1.4. The lipid bilayer membrane contains exchangers (top) and pumps that maintain appropriate ionic concentrations by shuttling specific ions in and out of the cell at the expense of energy (ATP). In addition, the cell membrane contains channels that let specific ions move in or out of the cell. These may be passive, meaning that they are stably open over time. Many channels are active, meaning that they can be either closed or open depending either on the potential across the cell membrane or in response to a ligand such as a neurotransmitter substance (green disc).

How does an electrical potential arise across the cell membrane? This can be intuitively understood from the description given above by considering a simple model. Assume that two compartments of a container are filled with an acqueous solution containing a chloride salt at different concentrations. Assume also that the two compartments are separated by an insulating membrane containing chloride channels, so that only chloride ions can flow across it. Initially, the membrane potential will be zero since there is no difference in electric charge across the membrane. However, chloride will start to flow down its concentration gradient and, since cations cannot pass the membrane, this will result in an electrical charge imbalance and thus an electrical membrane potential. Net flow will stop at equilibrium, when the membrane potential gradient exactly compensates for the concentration gradient across the membrane (fig. 1.5).



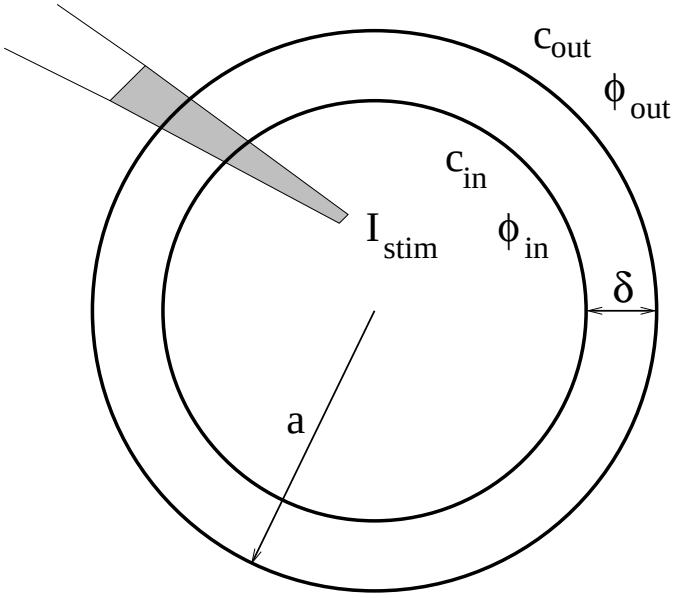

ions

**Figure** 1.5. Schematic illustration of how electrochemical potentials arise. If the membrane is specifically permeable to $Cl^-$ and not to associated cations, then diffusion of chloride across its concentration gradient will setup an associated electrical potential that will reach equilibrium when the diffusion and electrical gradients neutralize each other.

To formalize these arguments, we begin with the oversimplified geometry of a spherical cell and investigate the passive role its membrane plays as a leaky dielectric layer separating two conductors in the presence of exogenous current injection. To say that the cell is **isopotential** is to imply that the transmembrane potential difference, $V = \phi_{in} - \phi_{out}$, does not vary

in space. Our goal here is to derive an equation for the evolution of $V$ of with time.

We suppose our cell to have outer radius $a$ with a membrane of thickness $\delta$. We will focus here on the consequences of a concentration gradient of charged particles across the membrane. For example, typical values of the inner and outer concentration of chloride, $Cl^-$, in the squid giant axon are 0.04 and 0.56 Molar respectively. (1 Molar denotes 1 mole per liter). We will use the symbol $c(r)$ to denote the concentration of $Cl^-$ at radius $r$ for $a - \delta \leq r \leq a$.




geo

**Figure** 1.6. A cross section of a spherical cell with radius $a$ and membrane thickness $\delta$. The inner and outer concentrations are denoted $c_{in}$ and $c_{out}$ while the inner and outer potentials are denoted $\phi_{in}$ and $\phi_{out}$. We have also impaled the cell with an electrode ready to deliver the current $I_{stim}$.

nern

## 1.2. The Nernst Potential

As explained in the previous section, the gradients in both concentration and charge trigger associated Fickian and Ohmic fluxes through the membrane, respectively. Regarding the former, Fick's law states that the flux of matter across a surface is proportional to the concentration gradient,

i.e.,

$$J_{\text{Fick}}(r) = -D\frac{dc}{dr}(r) \tag{1.1}_{\text{fick}}$$

where $D$ (area/time) denotes diffusivity. This diffusivity is typically decomposed into $D = \mu kT$ where $T$ is temperature, $k$ is Boltzman's constant and $\mu$ denotes mobility. Ohm's law states that the flux of ions in solution across a surface is proportional to the potential gradient, to the charge density, and to mobility, i.e.,

$$J_{\text{Ohm}}(r) = -\mu zec(r)\frac{d\phi}{dr}(r) \tag{1.2}_{\text{ohm}}$$

where $z$ denotes the ion's valence ($z = -1$ for $\text{Cl}^-$) $e$ denotes the elementary electronic charge, and so $zec$ is a measure of charge density. The combined or net flux is therefore

$$J(r) = -\mu kT\frac{dc}{dr}(r) - \mu zec(r)\frac{d\phi}{dr}(r) \tag{1.3}_{\text{NP}}$$

This will now permit us to deduce the resting potential gradient from the resting concentration gradient. At rest we expect the net flux, $J$, to vanish. As such, we note that (1.3) takes the form

$$-kT\frac{d}{dr}(\log c(r)) = ze\frac{d\phi}{dr}(r).$$

We next integrate each side through the membrane, i.e., from $r = a - \delta$ to $r = a$, and arrive at

$$ze(\phi(a-\delta) - \phi(a)) = kT\log(c(a)/c(a-\delta)) \tag{1.4}_{\text{N-}}$$

In terms of in-out notation of Figure 1.6 and $V \equiv \phi_{in} - \phi_{out}$ Eq. (1.4) takes the form

$$V = \frac{kT}{ze}\log\frac{c_{out}}{c_{in}} \tag{1.5}_{\text{npot}}$$

At $T = 27^o\text{C}$ the leading coefficient is $kT/e = 25.8\ mV$. If $c$ is indeed pegged to chloride concentration then recalling that $z = -1$, $c_{in} = 0.04\ M$ and $c_{out} = 0.56$ we find

$$V_{Cl} = -68\ mV$$

for the value of the chloride **Nernst Potential**.

mcons

## 1.3. Membrane Conductance

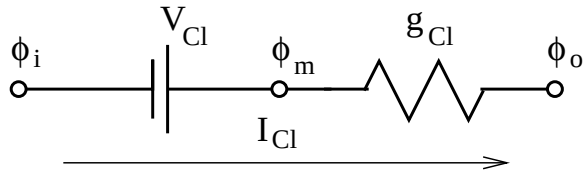
Now when the transmembrane potential, $V$, is different from $V_{Cl}$ we expect a flux of ions to cross the membrane and for an associated current to flow. Our goal here is to establish an associated membrane conductance. In fact the membrane is an insulating sheet perforated with a significant number of channels through which chloride ions may pass fairly easily. This conductor/insulator composite presents an effective bulk resistivity of

$$\rho_{Cl} = \frac{1}{3}10^{10}\ \Omega cm$$

to current flow. When scaled by the membrane thickness, e.g. $\delta = 10\ nm$, we arrive at the effective membrane conductance (per unit area)

$$g_{Cl} = \frac{1}{\rho_{Cl}\delta} = 0.3\ mS/cm^2$$

where $S$ is for *Siemens*, the reciprocal of $\Omega$. Next to $V_{Cl}$ it takes its place in the simple circuit diagram below.




mcon

**Figure** 1.7 The equivalent circuit model of the cell's leaky biased membrane. We have labeled the intermediate potential solely for clarity.

We may now use Ohm's law to represent the associated current density. We take potential differences in the direction of the arrow, namely, left to right. As such,

$$\phi_{in} - \phi_{mid} = V_{Cl}$$

and so

$$I_{Cl} = g_{Cl}(\phi_{mid} - \phi_{out}) = g_{Cl}(\phi_{in} - V_{Cl} - \phi_{out}) = g_{Cl}(V - V_{Cl}). \qquad (1.6)_{\text{ICl}}$$

The current density takes units of $\mu A/cm^2$.

mcap

## 1.4. Membrane Capacitance & Current Balance

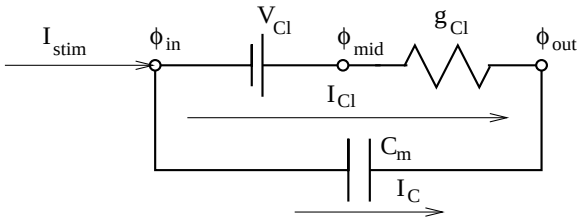
In addition to presenting significant resistance biological membranes form good dielectrics between their conducting surfaces. The effective dielectric constant, in Farads per cm, is

$$\varepsilon = 10^{-12}\ F/cm.$$

When scaled by the membrane thickness, $\delta = 10\ nm$, we arrive at the membrane capacitance

$$C_m = \varepsilon/\delta = 1\ \mu F/cm^2.$$

The associated displacement current operates in parallel with the Ohmic current.




mcap

**Figure** 1.8 The equivalent circuit model of the cell's leaky biased and dielectric membrane. These two currents will balance the injected current, $I_{stim}$.

The current density associated with a membrane capacitance is proportional to the rate of change of the potential across the capacitor. That is

$$I_C(t) = C_m \frac{d}{dt}(\phi_{in}(t) - \phi_{out}(t)) = C_m \frac{dV}{dt}(t) \qquad (1.7)_{\text{IC}}$$

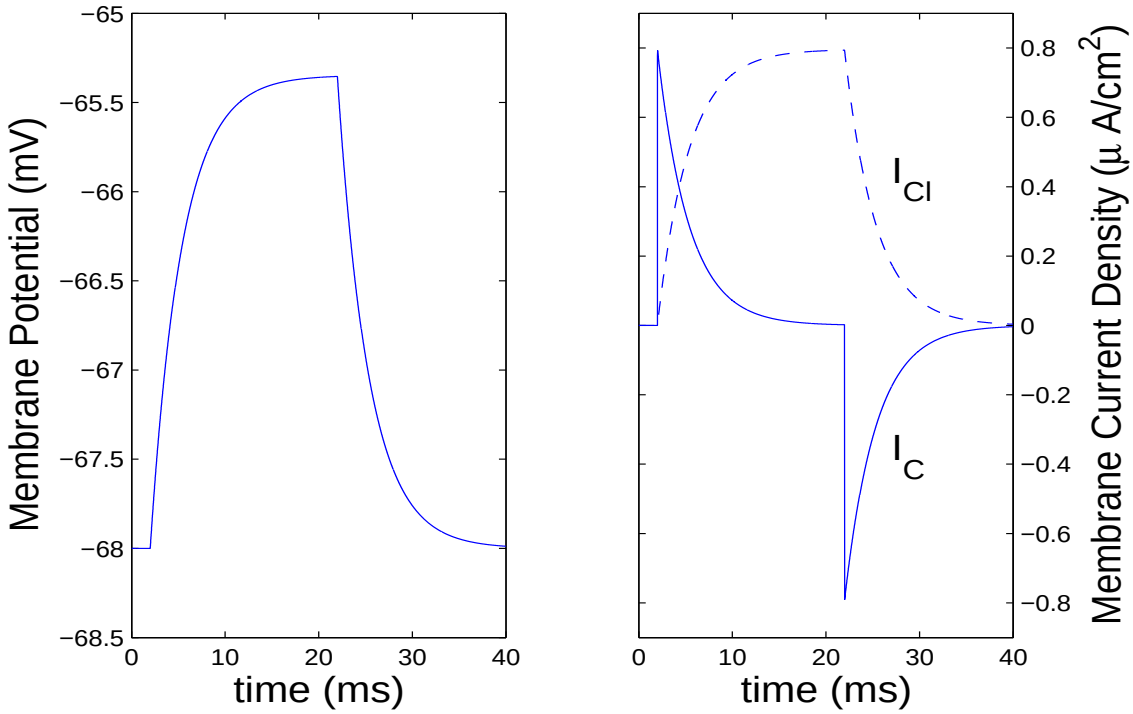
Our interest is in tracking how these two membrane currents respond to an injected pulse of current. In order to apply Kirchhoff's Current law we scale the membrane current densities by membrane surface area, $A$, and find

$$I_{stim}(t) = AI_C(t) + AI_{Cl}(t). \qquad (1.8)_{\text{kcl}}$$

On substituting (1.6) and (1.7) this becomes an ordinary differential equation for the membrane potential $V$. Namely,

$$I_{stim}(t) = AC_m V'(t) + Ag_{Cl}(V(t) - V_{Cl}). \qquad (1.9)_{\text{pode}}$$

We solve this starting from rest, i.e., $V(0) = V_{Cl}$, subject to a 10 $pA$ stimulus that turns on at 2 $ms$ and off at 22 $ms$, and for a cell of radius $a = 10\ \mu m$. In this case $A = 4\pi a^2 = 4\pi 10^{-6}\ cm^2$.




vresponse

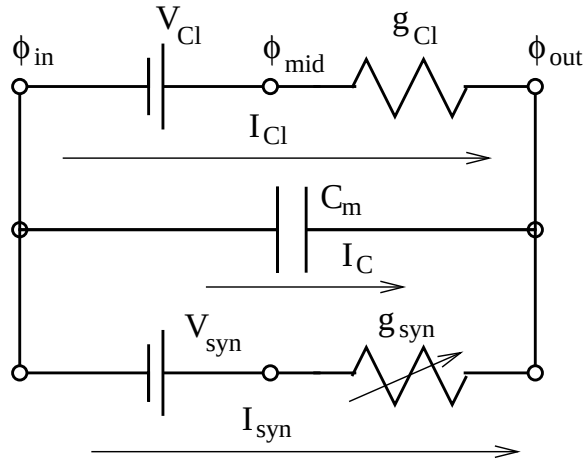
**Figure** 1.9. The solution (left) to (1.9) and the associated membrane currents (right) for a cell of radius 10 $\mu m$ subject to a 20 $ms$ 10 $pA$ current injection.

This model is indeed rich enough to replicate the passive response of actual cells. In coming chapters we shall spend considerable effort developing detailed models of more complicated membrane conductances. We shall see that many postsynaptic receptors behave like biased dynamic conductance changes.

syn1 **1.5. Synaptic Conductance**

The chloride conductance is the simplest of the membrane conductances. We shall see that there are many additional conductances that are either

gated by ligands, e.g., neurotransmitters, or by voltage, or by a combination of both.
This section is devoted to a first attack on the former. As the ligand gated membrane receptors bind and unbind neurotransmitter they produce a transient conductance change biased by an associated reversal potential. This is modeled by adding a third parallel branch to the membrane circuit of Figure 1.8




syn1

**Figure** 1.10. The circuit diagram for the passive cell with synapse. The arrow through the synaptic conductance is there to indicate that its conductance density varies with time.

Kirchhoff's Current Law, in the absence of injected current, now reveals that $V$ must satisfy

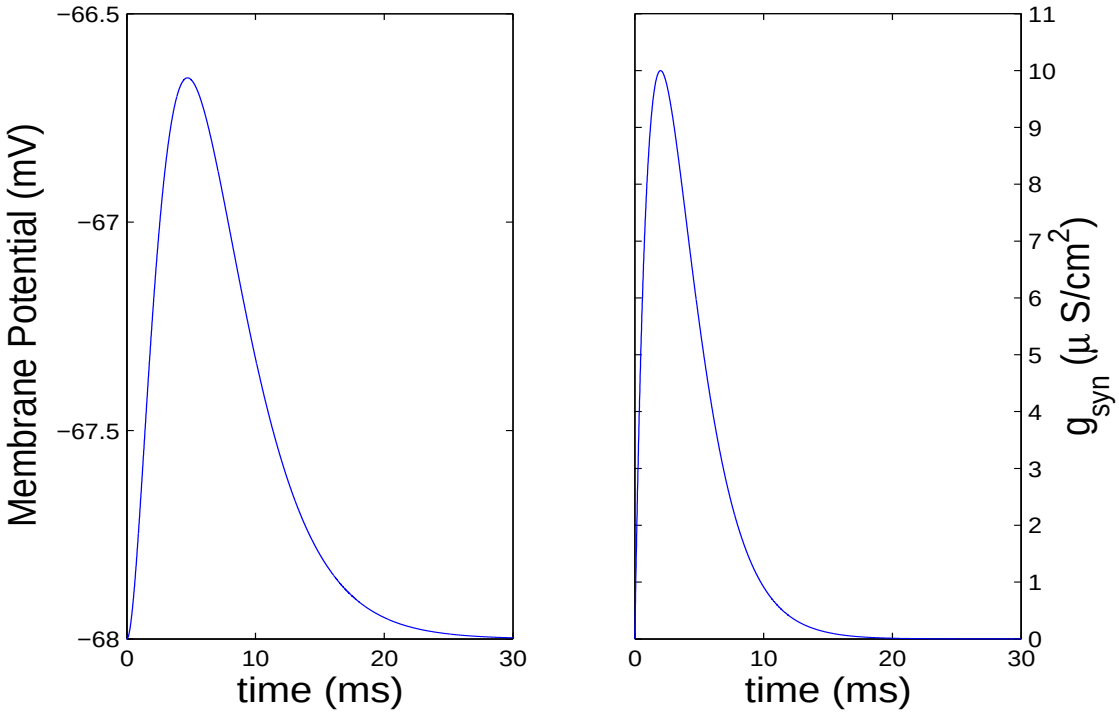
$$C_m V'(t) + g_{Cl}(V(t) - V_{Cl}) + g_{syn}(t)(V(t) - V_{syn}) = 0 \qquad (1.10)_{\text{psyn}}$$

Though we shall derive a number of functional forms for $g_{syn}(t)$ it will suffice here to note that $I_{syn}(t)$ typically rises faster than it decays and that the stereotypical response can be achieved by choosing $g_{syn}$ to be a so–called 'alpha' function,

$$g_{syn}(t) = g_{max}(t/\tau_\alpha)\exp(1 - t/\tau_\alpha) \qquad (1.11)_{\text{alpha}}$$

where $\tau_\alpha$ is the synaptic time constant ($ms$), and $g_{max}$ is the maximal conductance density ($mS/cm^2$).

If $V_{syn} > V_{Cl}$ then $I_{syn}$ will serve to increase (**depolarize**) $V$. In this case we call the synapse **excitatory**.
If $V_{syn} < V_{Cl}$ then $I_{syn}$ will serve to decrease (**hyperpolarize**) $V$. In this case we call the synapse **inhibitory**.




syn2

**Figure** 1.11. Response to excitatory synaptic input, $V_{syn} = 0$, $g_{max} = 0.01$ $(mS/cm^2)$ and $\tau_\alpha = 2$ $ms$.

## exe 1.6. Exercises

1. The stimulus used in Figure 1.9 is on long enough for the response $V$ to level off. Deduce from Eq. (1.9) the maximum value of $V$. Hint: $V'(t) = 0$ there.

2. Regarding the $g_{syn}$ of Eq. (1.11), compute (i) its maximum value and the time at which it attains this value, and (ii) its integral over all time.

3. Most cells receive both excitatory and inhibitory input. Draw the circuit diagram (analogous to Figure 1.10) and express KCL as an ordinary differential equation (analogous to Eq. (1.10)) in the case that our spherical cell receives both excitatory input with conductance $g_E(t)$ and associated potential $V_E$ and inhibitory input with conductance $g_I(t)$ and associated potential $V_I$.

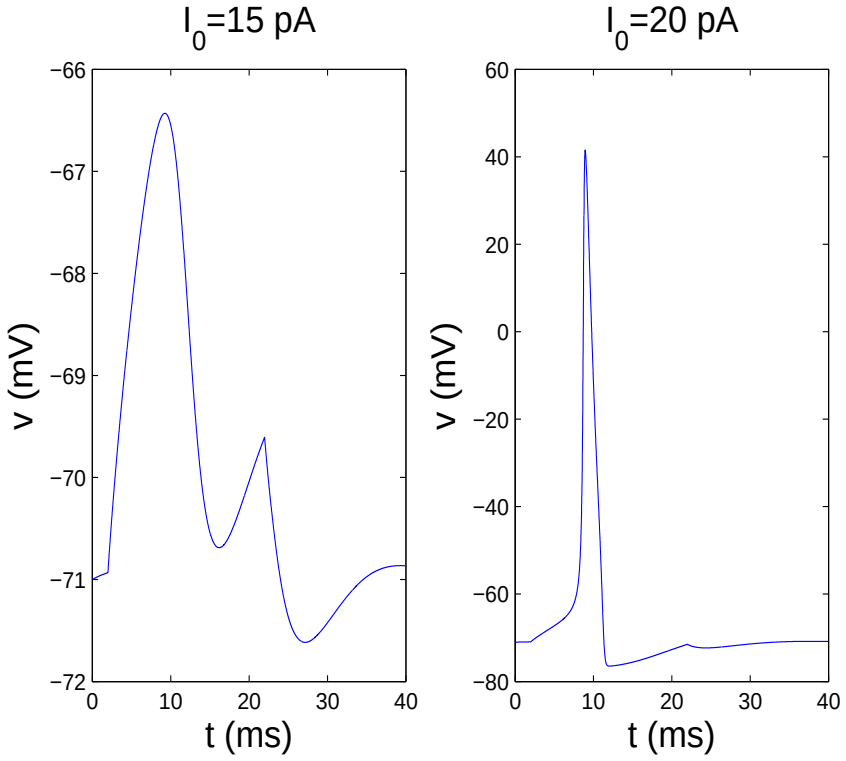
act

# 2. The Active Isopotential Cell

The passive model constructed in chapter 1 provides a fairly accurate prediction of the cell's response to 'small' current and/or synaptic input. For larger inputs this model however fails to reproduce the observed 'action potential.' For example, if we presume a stimulus of the form

$$I_{stim}(t) = (t > 2)(t < 22)I_0$$

and we adopt the membrane model of Hodgkin and Huxley we would expect the response to change abruptly as the amplitude, $I_0$, exceeds approximately 16 $pA$. We depict this scenario below.

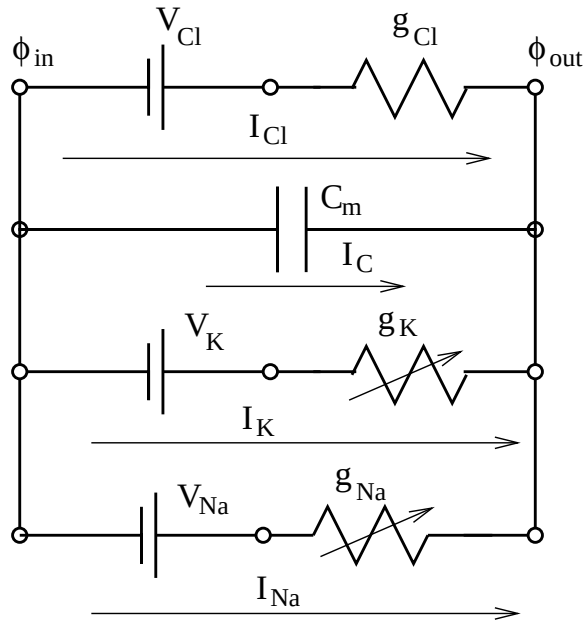



vthresh

**Figure** 2.1 Response of the active cell to subthreshold (left) and suprathreshold (right) current stimuli.

Following Hodgkin and Huxley, the action potential is understood as the product of voltage–gated conductances that permit the coordinated influx

of sodium, $Na^+$, and the eflux of potassium, $K^+$. As with chloride, the respective concentration gradients beget associated Nernst potentials, and we are compelled to consider a more complex circuit diagram.




hhcirc

**Figure** 2.2 The equivalent circuit model of the cell's active membrane.

As these channels are not entirely closed at rest, the resting potential is not simply $V_{Cl}$. We shall eventually derive a formula for it, but for now we suppose the **resting potential** to be some measured value, $V_r$. It is very convenient, when deriving equations that start from rest, to choose variables with respect to rest. To wit, we denote our new dependent variable by

$$v = V - V_r$$

and our three new membrane batteries by

$$v_{Na} = V_{Na} - V_r, \quad v_K = V_K - V_r, \quad \text{and} \quad v_{Cl} = V_{Cl} - V_r.$$

gK

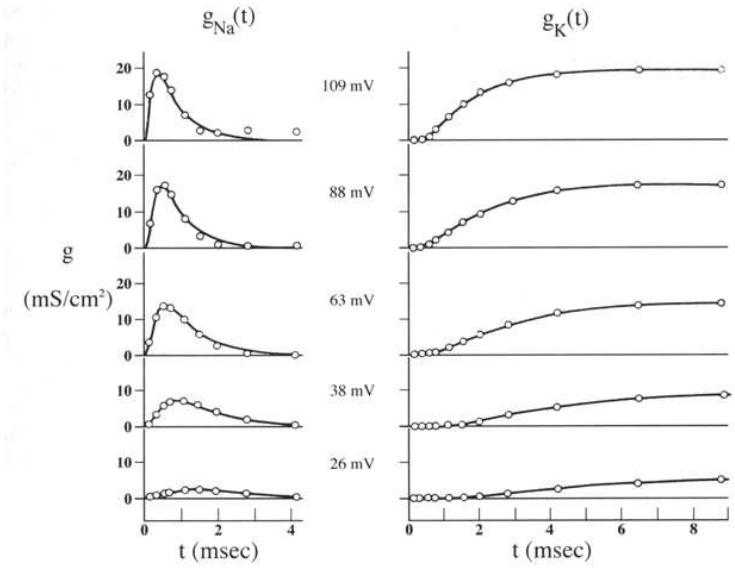
## 2.1. The Potassium Channel

Hodgkin and Huxley observed that the potassium conductance varied with time and voltage. At a fixed voltage however they observed that the con-

ductance grew monotonically in time to a steady level (fig. 2.3, right). They therefore postulated a potassium conductance of the form

$$g_K = \overline{g}_K n^4(t; v) \qquad (2.1)_{\text{gK}}$$

where $\overline{g}_K$ is the conductance/area of open $K^+$ channels $n(t; v)$ is the probability that a $K^+$ channel is open at time $t$.




hhres

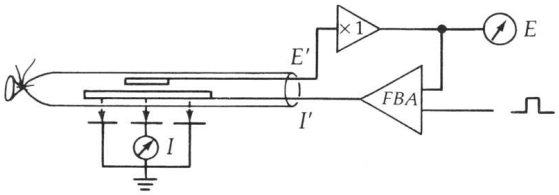
**Figure** 2.3. Time course of the sodium (left) and potassium (right) conductances measured by Hodgkin and Huxley in the giant squid axon as the membrane potential was stepped to a constant value above rest (labels in the middle). The points represent experimental data, the solid lines represent the fits of their model as explained in the text.

To say that $n$ approaches a steady (voltage dependent) level $n_\infty(v(t))$ at the (voltage dependent) rate $\tau_n(v(t))$ is to ask that

$$n'(t) = \frac{n_\infty(v(t)) - n(t)}{\tau_n(v(t))} \qquad (2.2)_{\text{dn}}$$

Hodgkin and Huxley determined the exponent, 4, and the functional forms of $n_\infty$ and $\tau_n$ via an ingenious combination of theory and experiment. Regarding the latter, they could chemically and electrically rig their (squid

giant axon) preparation in such a way that $I_K$ was the only current. This meant doctoring the bath to eliminate other ions, inserting a long conductor to thwart spatial effects and, most importantly, using a **voltage clamp** to simultaneously thwart the capacitive current and so measure the $K^+$ current over a range of physiological voltages. More precisely, they could clamp the voltage to $V_c$ and record the current necessary to maintain the clamp (fig. 2.4). As $I_K$ was the only uninterrupted current their measured current was indeed $I_K$.




hhschem

**Figure** 2.4. Schematic illustration of the voltage clamp setup of Hogdkin and Huxley. The giant axon is sealed at one end. Both the intra- and extracellular fluids and ionic concentrations are controlled. An electrode is placed inside the giant axon to measure potential with respect to the extracellular fluid (top, $E'$). The potential is read on a voltmeter ($E$). An amplifier ($FBA$) is used to compare the measured potential with the desired one (command pulse), the difference determines the injected current ($I'$) necessary to compensate any changes. The resulting membrane current is measured using an ampmeter ($I$).

If we denote by $\{t_1, t_2, \ldots, t_N\}$ the times at which the current was measured then we can invert Ohm's law and find

$$g_K(t_j; v_c) = I_K(t_j)/(V_c - V_K) \quad j = 1, \ldots, N$$

Now, in order to reconcile this with Eq. (2.1) we note that with $v(t) = v_c$ in Eq. (2.2) that

$$n(t; v_c) = n_\infty(v_c) + \exp(-t/\tau_n(v_c))(n_\infty(0) - n_\infty(v_c)). \qquad (2.3)_{\text{nc}}$$

They first eye-ball

$$\overline{g}_K = 24.31 \quad \text{and} \quad g_K(0; v_c) = 0.24$$

and then argue that

$$n_\infty(0) = (g_K(0; v_c)/\overline{g}_K)^{1/4} \quad \text{and} \quad n_\infty(v_c) = (g_K(t_N; v_c)/\overline{g}_K)^{1/4}.$$

This leaves only $\tau_n(v_c)$ remaining. They determine it by minimizing

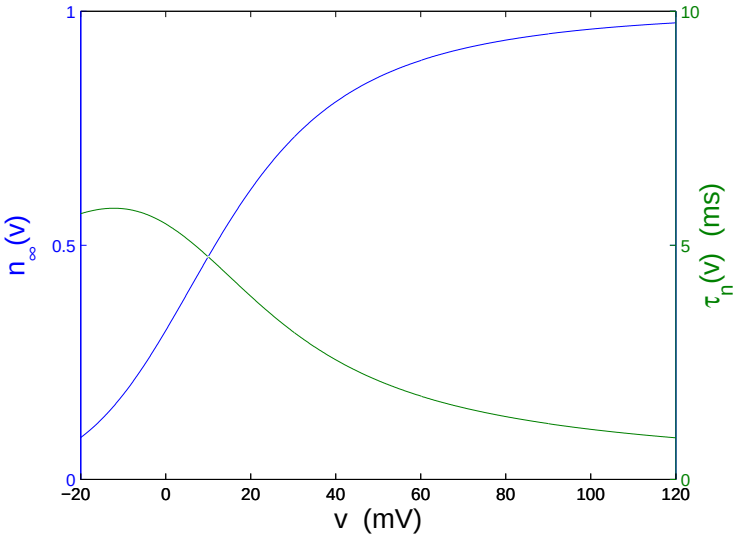
$$\Phi(\tau; v_c) = \frac{1}{N}\sum_{j=1}^{N}(\overline{g}_K(n_\infty(v_c) + \exp(-t_j/\tau)(n_\infty(0) - n_\infty(v_c))^4 - g_K(t_j; v_c))^2$$

over $\tau$ at each $v_c$. They then parametrize these functionals in terms of

$$\tau_n(v) = \frac{1}{\alpha_n(v) + \beta_n(v)} \quad \text{and} \quad n_\infty(v) = \alpha_n(v)\tau_n(v)$$

where

$$\alpha_n(v) = \frac{.01(10 - v)}{\exp(1 - v/10) - 1} \quad \text{and} \quad \beta_n(v) = \exp(-v/80)/8$$




nfig

**Figure** 2.5. The gating functions that govern the potassium channel.

gNa

## 2.2. The Sodium Channel

With sodium back in the bath the response is considerably different. The conductance rises and falls (fig. 2.3, left). Hodgkin and Huxley chose to model this via two, independent, voltage driven processes. At a fixed voltage however Hodgkin and Huxley observed that the conductance grows and then decays. They therefore postulated a sodium conductance of the form

$$g_{Na} = \overline{g}_{Na} m^3(t;v) h(t;v) \qquad (2.4)_{\text{gna}}$$

where the activation (growth) variable, $m$, and inactivation (decay) variable, $h$, obey, as in (2.2)

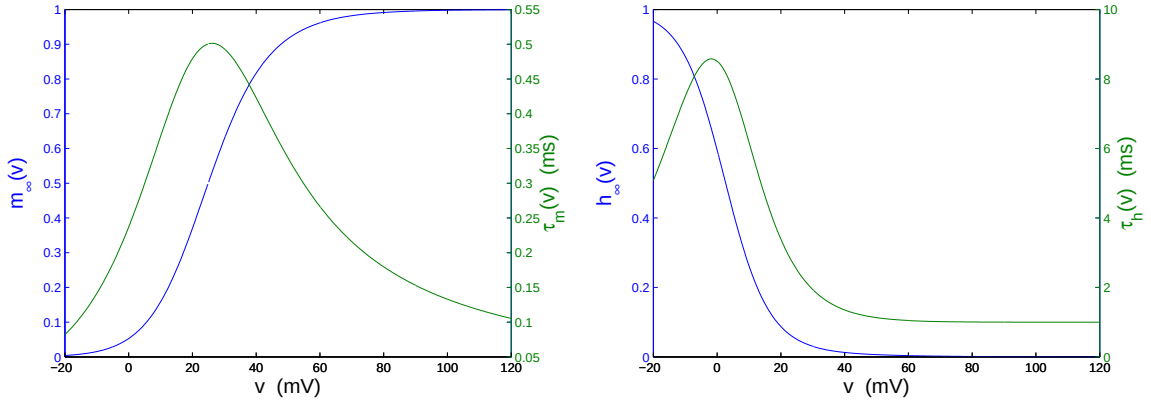
$$m'(t) = \frac{m_\infty(v(t)) - m(t)}{\tau_m(v(t))} \quad \text{and} \quad h'(t) = \frac{h_\infty(v(t)) - h(t)}{\tau_h(v(t))}$$

As above if the membrane potential is held at $v_c$ (with respect to rest) then we may solve these for $m(t;v_c)$ and $h(t;v_c)$ and fit Eq. (2.4) to the measured clamp current and arrive at

$$\tau_m(v) = \frac{1}{\alpha_m(v) + \beta_m(v)} \quad \text{and} \quad m_\infty(v) = \alpha_m(v)\tau_m(v)$$
$$\tau_h(v) = \frac{1}{\alpha_h(v) + \beta_h(v)} \quad \text{and} \quad h_\infty(v) = \alpha_h(v)\tau_h(v)$$

where

$$\alpha_m(v) = .1(25 - v)/(\exp(2.5 - v/10) - 1) \quad \text{and} \quad \beta_m(v) = 4\exp(-v/18)$$
$$\alpha_h(v) = 0.07\exp(-v/20) \quad \text{and} \quad \beta_h(v) = 1/(\exp(3 - v/10) + 1)$$



mhfig

**Figure** 2.6. The gating functions that govern the sodium channel.

HHE

## 2.3. The Hodgkin–Huxley Equations

Adopting the squid parameters from Hodgkin and Huxley,

$$V_K = -77\,mV, \quad \overline{g}_K = 36mS/cm^2, \quad V_{Na} = 56\,mV \quad \text{and} \quad \overline{g}_{Na} = 120mS/cm^2$$

we may know calculate the rest potential. For, at rest, membrane current

$$\overline{g}_K n^4(0)(V_r - V_K) + \overline{g}_{Na} m^3(0)h(0)(V_r - V_{Na}) + \overline{g}_{Cl}(V_r - V_{Cl})$$

must vanish and so

$$V_r = \frac{\overline{g}_K n^4(0)V_K + \overline{g}_{Na} m^3(0)h(0)V_{Na} + \overline{g}_{Cl}V_{Cl}}{\overline{g}_K n^4(0) + \overline{g}_{Na} m^3(0)h(0) + \overline{g}_{Cl}} \approx -71\ mV.$$

It follows that

$$v_K = -6, \quad v_{Na} = 127, \quad \text{and} \quad v_{Cl} = 2.8417 \qquad (2.5)_{\text{newnernst}}$$

We now have all of the components of the (isopotential) Hodgkin-Huxley system,

$$\begin{aligned} C_m v'(t) &= -\overline{g}_{Na} m^3 h(v - v_{Na}) - \overline{g}_K n^4 (v - v_K) \\ &\quad - \overline{g}_{Cl}(v - v_{Cl}) + I_{stim}/A \qquad (2.6)_{\text{iHHv}} \\ n'(t) &= \alpha_n(v)(1-n) - \beta_n(v)n \qquad (2.7)_{\text{iHHn}} \\ m'(t) &= \alpha_m(v)(1-m) - \beta_m(v)m \qquad (2.8)_{\text{iHHm}} \\ h'(t) &= \alpha_h(v)(1-h) - \beta_h(v)h \qquad (2.9)_{\text{iHHh}} \end{aligned}$$

With $\mathtt{v}_j \approx v(jdt)$ the backward Euler scheme produces

$$\begin{aligned} C_m(\mathtt{v}_j - \mathtt{v}_{j-1})/dt &= -\overline{g}_{Na}\mathtt{m}_j^3\mathtt{h}_j(\mathtt{v}_j - v_{Na}) - \overline{g}_K\mathtt{n}_j^4(\mathtt{v}_j - v_K) - \overline{g}_{Cl}(\mathtt{v}_j - v_{Cl}) + I_j/A \\ (\mathtt{n}_j - \mathtt{n}_{j-1})/dt &= \alpha_n(\mathtt{v}_j)(1 - \mathtt{n}_j) - \beta_n(\mathtt{v}_j)\mathtt{n}_j \\ (\mathtt{m}_j - \mathtt{m}_{j-1})/dt &= \alpha_m(\mathtt{v}_j)(1 - \mathtt{m}_j) - \beta_m(\mathtt{v}_j)\mathtt{m}_j \\ (\mathtt{h}_j - \mathtt{h}_{j-1})/dt &= \alpha_h(\mathtt{v}_j)(1 - \mathtt{h}_j) - \beta_h(\mathtt{v}_j)\mathtt{h}_j \end{aligned}$$

One must solve this **nonlinear** system to move from $(j-1)dt$ to $jdt$. This can be relaxed by a seemingly small change, namely, "evaluate the gating functions at the previous, rather than present, voltage." This produces

$$(\mathtt{m}_j - \mathtt{m}_{j-1})/dt = \alpha_m(\mathtt{v}_{j-1})(1-\mathtt{m}_j) - \beta_m(\mathtt{v}_{j-1})\mathtt{m}_j$$

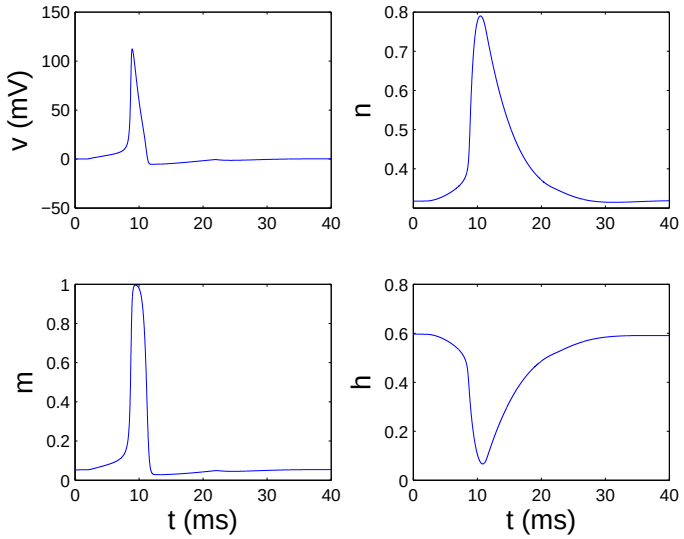
and so each gating variable may be **explicitly** represented

$$\mathtt{m}_j = \frac{\mathtt{m}_{j-1} + \alpha_m(\mathtt{v}_{j-1})dt}{1 + (\alpha_m(\mathtt{v}_{j-1}) + \beta_m(\mathtt{v}_{j-1}))dt} \qquad (2.10)_{\text{mexact}}$$

and so finally

$$\mathtt{v}_j = \frac{C_m\mathtt{v}_{j-1} + (\overline{g}_{Na}\mathtt{m}_j^3\mathtt{h}_j v_{Na} + \overline{g}_K\mathtt{n}_j^4\mathtt{v}_K + \overline{g}_{Cl}v_{Cl} + I_j/A)dt}{C_m + (\overline{g}_{Na}\mathtt{m}_j^3\mathtt{h}_j + \overline{g}_K\mathtt{n}_j^4 + \overline{g}_{Cl})dt}$$

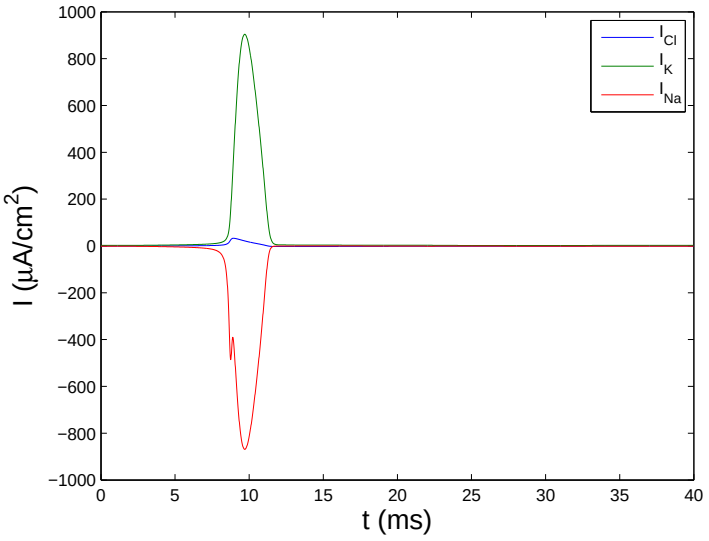
We have code this mixed, or hybrid, Euler in `heas.m`. If we deliver a 20 $pA$ current for a few milliseconds it reveals




actives

**Figure** 2.7. The action potential and its gating variables.

This $v$ is indeed the one foreshadowed in Figure 2.1. Its upstroke is facilitated by $m$ while its downstroke comes thanks to $n$ and $h$. These variables are fundamental components of the individual ionic currents.




actives

**Figure** 2.8. The associated membrane currents.

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## 2.4. Exercises

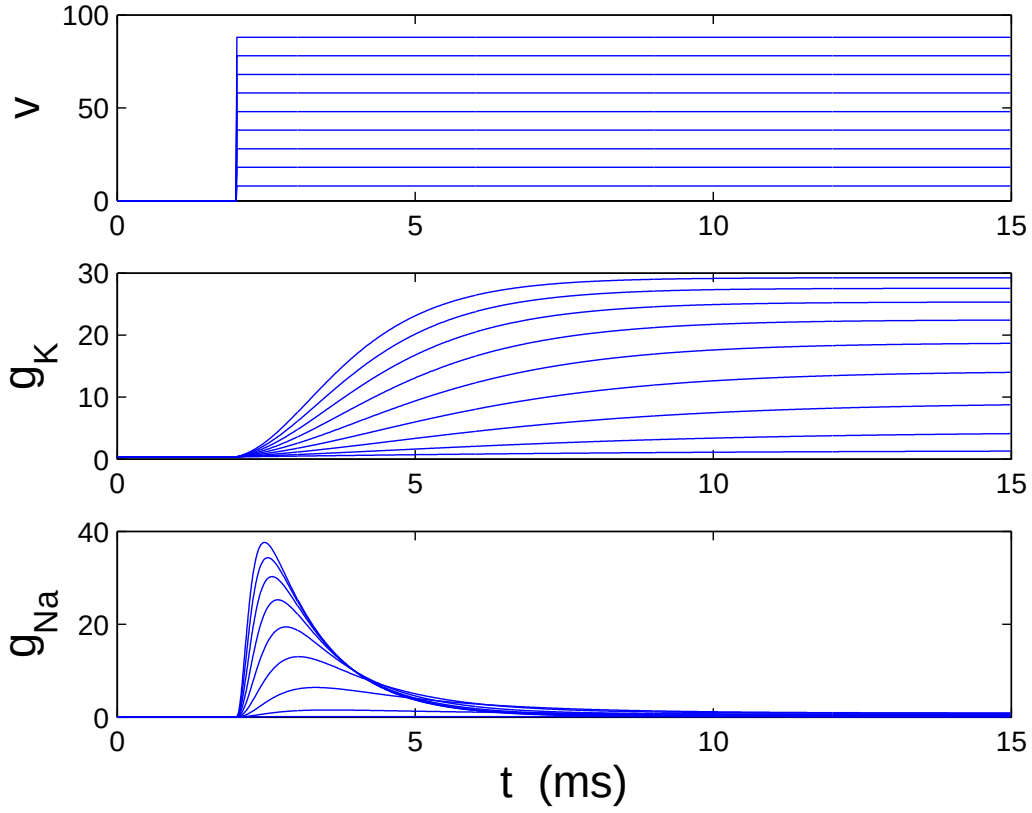
1. Let us attempt to simulate the **voltage–clamp** experiments of Hodgkin and Huxley. More precisely, suppose

$$v(t) = (t > 2)(t < 15)v_c,$$

where $v_c$ is the desired clamp potential, and modify `heas.m` to solve for the associated gating variables and plot (as below) $v$ and

$$g_K(t) = \overline{g}_K n^4(t) \quad \text{and} \quad g_{Na}(t) = \overline{g}_{Na} m^3(t) h(t)$$

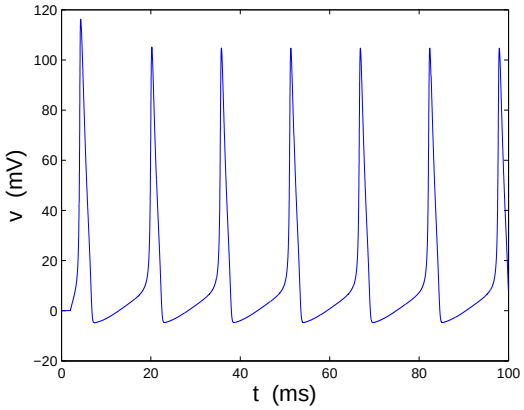
for a range of clamp potentials. Submit your code and your figure.

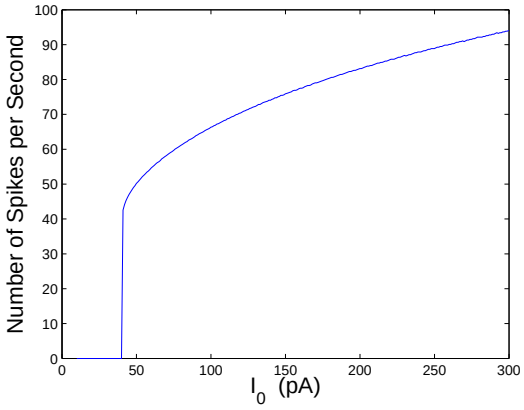



2. The next two exercises will help us understand the rate at which our cell may fire. To begin, modify `heas.m` to deliver two brief current pulses. In particular, take $I_0 = 30\ pA$, deliver a $4\ ms$ pulse beginning at $2\ ms$ and deliver the second $4\ ms$ beginning at $t_2\ ms$. Find (to

2 digits of accuracy) the time threshold $t_R$ for which the cell spikes twice when $t_2 > t_R$. We call this time span, during which the cell is insensitive to further input, its **refractory period.** Submit your code, your value of $t_R$, and two voltage plots (corresponding to $t_2$ on either side of $t_R$).

3. We notice that for sustained current input that our cell enters a regime of periodic firing. For example, if $I_{stim} = 100(t > 2)\ pA$ we observe the response below (left).




Your task is to modify `heas.m` to deliver sustained currents and to count the number of spikes per second. Submit your code and figure of the form above (right).

4. The firing rate diagram of the previous exercise may be modified by the inclusion of additional channel types. There are multiple types of $K$ channels. We proceed by studying one that inactivates,

$$I_A = \overline{g}_A a^3 b(V - V_A), \quad a'(t) = \frac{a_\infty(V) - a}{\tau_a(V)} \quad b'(t) = \frac{b_\infty(V) - b}{\tau_b(V)}$$

where

$$a_\infty(V) = \left(\frac{0.0761\exp(0.0314(V + 94.22))}{1 + \exp(0.0346(V + 1.17))}\right)^{1/3}$$

$$\tau_a(V) = 0.3632 + \frac{1.158}{1 + \exp(0.0497(V + 55.96))}$$

$$b_\infty(V) = \frac{1}{(1 + \exp(0.0688(V + 53.3)))^4} \quad \tau_b(V) = 1.24 + \frac{2.678}{1 + \exp(0.0624(V + 50))}$$

We also consider modified $Na$ and $K$ functionals

$$\alpha_n(V) = \frac{.02(v+45.7)}{1-\exp(-(v+45.7)/10))} \quad \beta_n(V) = .25\exp(-0.0125(v+55.7))$$
$$\alpha_m(V) = \frac{0.38(v+29.7)}{1-\exp(-(v+29.7)/10))} \quad \beta_m(V) = 15.2\exp(-0.0556(v+54.7))$$
$$\alpha_h(V) = 0.266\exp(-0.05(v+48)) \quad \beta_h(V) = \frac{3.8}{1+\exp(-(v+18)/10))}$$

With absolute reversal potentials, $(mV)$, $V_K = -72$, $V_A = -75$, $V_{Na} = 55$, $V_L = -17$ and maximal conductances, $(mS/cm^2)$, $\overline{g}_K = 20$, $\overline{g}_{Na} = 120$, $\overline{g}_A = 47.7$ and $\overline{g}_L = 0.3$ we find rest at $V_r = -68$.

5. Returning to Figure 2.8 we pursue a pair of simple observations. First, $m$, the gating variable of sodium activation is so fast that perhaps we can simply presume that it instantaneously reaches its steady state level, $m_\infty(v(t))$. That is

$$m(t) \approx m_\infty(v(t)).$$

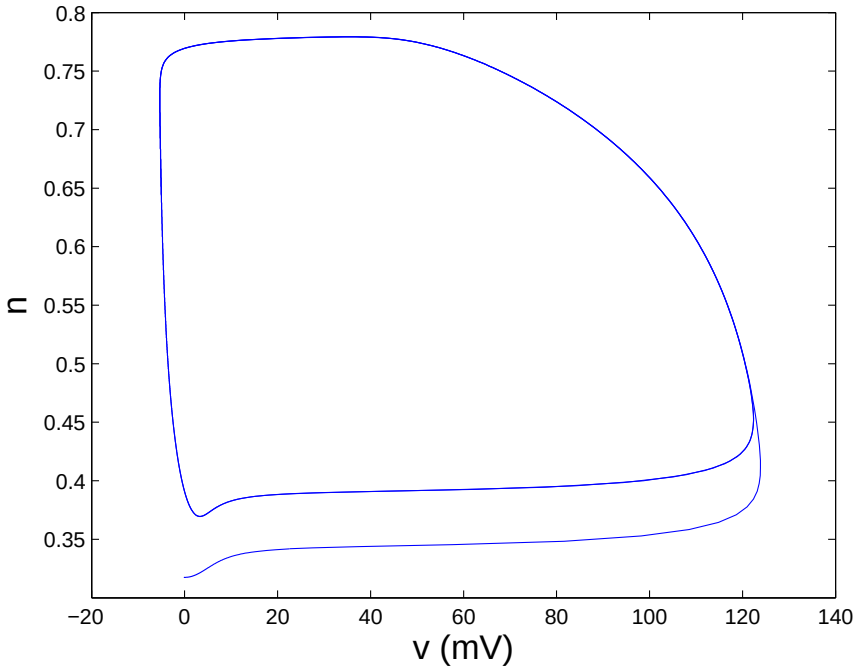
Second, we observe that $n + h$ is fairly flat. In, particular.

$$h(t) \approx 0.87 - n(t).$$

With these approximation, the Hodgkin-Huxley system (2.6)–(2.9) reduces to

$$\begin{aligned} C_m v'(t) &= -\overline{g}_{Na} m_\infty^3(v)(0.87-n)(v-v_{Na}) - \overline{g}_K n^4(v-v_K) \\ &\quad - \overline{g}_{Cl}(v-v_{Cl*}) + I_{stim}/A \\ n'(t) &= \alpha_n(v)(1-n) - \beta_n(v)n \end{aligned}$$

where $v_{Cl*} = 3.1716$ has been chosen so that rest remains at $v = 0$, $n = n_\infty(0)$. Modify `heas.m` to solve this two–variable reduced system and graph its response to $I_{stim} = 50(t > 2)\ pA$ in the 'phase plane' as depicted below.




Submit your code and the resulting figure.